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OTOLOGY

Clinical features and management of Meniere's disease patients with drop attacks

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Abstract

Purpose The aims of the present study are to investigate the variations in clinical features, including medical history, hearing function, vestibular function, and degree of endolymphatic hydrops (EH), in Meniere's disease (MD) patients with and without drop attacks (DAs), and to examine the efficacy of intratympanic gentamicin (ITG) treatment in alleviating DAs.

Methods In total, 177 unilateral definite MD patients, including 16 patients with DAs and 161 patients without DAs, were enrolled. The results of hearing test, vestibular-evoked myogenic potentials (VEMPs), and magnetic resonance imaging (MRI) were analyzed. Thirteen patients with DAs received a single ITG treatment and were followed up.

Results The disease course of MD in the DA group was significantly longer than that in the control group ($p = 0.007$). MD patients with DAs had significantly greater hearing loss and worse EH than MD patients without DAs ($p < 0.05$). However, there was no between-group difference in vestibular function. In the study, 92.31% of refractory definite MD patients with DAs achieved satisfactory control of DAs after ITG treatment.

Conclusions MD patients with DAs tend to suffer from severe hearing loss and a significant degree of EH in the inner ear. However, the vestibular function of MD patients with DAs may not be completely abolished, but be sensitive to stimulating signals. ITG treatment, which helps to decrease vestibular sensitivity, was an effective treatment to control DAs.

Keywords Tumarkin attack · Vertigo · Endolymphatic hydrops · Otolithic organ

Introduction

As we know, Meniere's disease (MD) is a refractory inner ear disorder characterized by spontaneous attacks of vertigo, fluctuating sensorineural hearing loss, tinnitus and ear fullness. A small number of MD patients were suffering from a life threatening sudden fall named as drop attacks (DAs). DAs associated with Meniere's disease (MD) was initially described as an "otolithic catastrophes" by Tumarkin in 1936 [1]. This kind of sudden fall, which is known as "Tumarkin's otolithic crisis" or "Tumarkin attack (TA)", occurs without warning and without loss of consciousness but happens to patients with a history of Meniere's disease.

Although previous studies revealed that the incidence of DAs was lower than 10% in MD patients [2–4], sudden onset of DA may occur in individuals with MD at any time in daily life. The risk of injury due to sudden falls without warning gives rise to fear. As yet, few clinical reports have provided comprehensive comparisons of MD patients with and without DAs to figure out the clinic feature of DAs patients. Endolymphatic hydrops (EH) is demonstrated by temporal bone histopathology [5] and specific magnetic resonance imaging (MRI) of the inner ear [6] in MD patients. It is considered as the main histopathological marker of MD [7]. Sudden stimulation of an injured otolithic membrane of the utricle and/or saccule caused by an unstable endolymphatic pressure gradient within the inner ear is thought to be a key trigger of DAs in MD patients [3]. However, to our best knowledge, there have been no studies aimed at revealing the degree of EH in the inner ear of MD patients with DAs. We presume that the degree of EH in the inner ear may affect

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utricular and saccular function and be associated with hearing loss and the onset of DAs in MD patients. In this case, MD patients with DAs may have a greater EH in the inner ear than patients without DAs.

A better understanding of the differences in clinical features of MD patients with and without DAs would enable the selection of more aggressive and efficient treatment. Various treatments for MD, such as conservative treatment [8], labyrinthectomy, endolymphatic shunt operation, vestibular neurectomy [2], intratympanic steroids injection [9], and intratympanic gentamicin (ITG) injection [10], have been proposed for the management of MD patients with DAs. The optimum management for MD patients with DAs remains to be determined. ITG treatment has been reported to achieve a high vertigo control rate ranged from 80.7 to 89.5% [11–14] since aminoglycoside was first applied to treat refractory MD patients by Schuknecht [15]. The mechanism underlying vertigo control of MD patients after ITG is that gentamicin damages the vestibular neuroepithelium and decreases the sensitivity of vestibule [16, 17]. DAs result from stimulation to an injured otolithic membrane of the otolithic organ. We hypothesize that ITG, which decreases vestibular function, may also be an effective treatment to alleviate the symptom of DAs.

Therefore, the aims of this study are to retrospectively investigate variations in clinical features (medical history, hearing function, vestibular function, and the degree of EH in each part of the inner ear) in MD patients with and without DAs, and to examine the efficacy of ITG treatment in alleviating vertigo-related symptoms and DAs.

Materials and methods

Patients

From a database of 209 MD patients diagnosed between May 2013 and July 2017, 177 unilateral definite MD patients, including 16 patients with DAs and 161 patients without DAs, were enrolled in the present study. All individuals were clinically diagnosed with definite MD on the basis of the criteria proposed by the 2015 Classification Committee of the Barany Society [18] (Table 1). All examinations were conducted in the Department of Otology and Skull Base Surgery of the Eye, Ear, Nose and Throat Hospital, Fudan University.

The MD patients were divided into definite MD patients without DAs (the control group) and definite MD patients with DAs (DA group). The inclusion criteria for MD patients in the DA group are illustrated in Table 1. All patients were asked to perform the hearing test and vestibular-evoked myogenic potentials (VEMPs) after being collected medical history. Meanwhile, EH was confirmed in all MD patients using MRI following a bilateral intratympanic gadolinium (Gd) injection. ITG treatment was discussed with unilateral definite MD patients with DAs after diagnosis.

The present study was approved by the medical ethics committee of the eye, ear, nose & throat hospital, and all the MD patients signed the informed consent.

Audiometric assessment

Hearing thresholds, including air and bone conduction at all frequencies (0.125–8 kHz) in bilateral ears, were tested in all MD patients. The pure tone average (PTA) threshold was evaluated based on 0.5, 1, 2, and 3 kHz. Hearing levels at low (125–250 Hz), middle (500–2000 Hz), and high (4–8 kHz) frequencies were calculated separately. The hearing threshold at 3 kHz was the mean hearing threshold at 2 and 4 kHz.

VEMPs

The cervical vestibular-evoked myogenic potential (cVEMP) and the ocular vestibular-evoked myogenic potential (oVEMP) were tested as described previously [19]. Briefly, air-conducted sound with a short tone burst (2-ms rise/fall time and 2-ms plateau time) at 500 Hz was used as an auditory stimulus. The starting stimulus intensity was 95 dB nHL and this was decreased with each 5 dB nHL until the VEMP response was abolished. This process was repeated three times. The cVEMP was identified when the

Table 1 The inclusion criteria for Meniere's disease patients

Definite Meniere's disease	Meniere's disease patients in drop attack group
A. Two or more spontaneous episodes of vertigo, each lasting 20 min to 12 h	A. Untreated unilateral definite disease
B. Audiometrically documented low- to medium frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo	B. At least one sudden fall without loss of consciousness and without warning
C. Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear	C. No history of middle ear diseases, neurological disorders, cardiovascular abnormalities, muscle disorders, or other vertigo disorders
D. Not better accounted for by another vestibular diagnosis	

first positive–negative–positive wave peak (P1–N1–P2) appeared. The oVEMP was recorded when the first negative and positive biphasic wave peak (N1–P1) appeared. If the waveforms could not be recognized or were not repeatable, the absence of cVEMP or oVEMP was confirmed. The characteristics of the VEMPs including threshold values were recorded.

Evaluation of EH following an intratympanic injection of Gd

Gd was administered via a bilateral intratympanic injection in all MD patients using a 22-gauge spinal needle and a 1-ml syringe. The contrast agent was diluted eightfold with saline (v/v 1:7). About 0.5 ml of diluted Gd solution was injected through the tympanic membrane with the aid of an otoendoscope until the tympanic cavity was filled. The patients were asked to remain in a supine position, with their head 45 degrees toward the unaffected side for 30 min without speaking or swallowing. MRI images were harvested with a 3T unit (Verio, Siemens) using a 32-channel phased array receive-only coil 24 h after the bilateral intratympanic Gd injection. For image collection, the T2 space and three-dimensional real inversion recovery (3D-real IR) sequences were used. Details on the MRI parameters applied herein have been described previously [20].

All the images obtained by MRI were evaluated by an experienced radiologist who was blinded to the diagnosis of all patients. The T2 space sequence was used to exclude other middle ear and neurological disorders. An enlarged endolymphatic space was considered a large negative signal dilating to the contrast-enhanced signal of the perilymphatic space. The degrees of EH in the vestibule and cochlea of inner ear were classified into three stages: none, mild, and significant, according to the criteria proposed by Nakashima et al. [21]. In the vestibule, the grading was determined by the area ratio of the endolymphatic space to the vestibular fluid space (sum of the endolymphatic and perilymphatic spaces). Patients with no hydrops had a ratio of one-third or less, those with mild hydrops had between one-third and half, and those with significant hydrops had a ratio of more than half. In the cochlea, patients with no hydrops showed no displacement of Reissner's membrane. Those with mild cochlear hydrops showed displacement of Reissner's membrane, but the area of the endolymphatic space did not exceed the area of scala vestibuli. In those with significant cochlear hydrops, the area of the endolymphatic space exceeded the area of scala vestibuli. Each turn of the cochlea was evaluated on the basis of the criteria. Adobe Photoshop CC 2017 (Adobe, San Jose, CA) was applied to calculate the ratio of the area of the endolymphatic space to the entire saccular and utricular space which represented the degree of vestibular EH.

Outcomes in MD patients with DAs following ITG treatment

Thirteen unilateral definite MD patients with DAs received a single intratympanic injection of 30 mg/ml of gentamicin (1.5 ml of 40 mg/ml of gentamicin sulfate diluted with 0.5 ml of 50 mg/ml $NaHCO_3$ solution) to the affected ears, as described above. Three of the 16 enrolled patients with DAs underwent conservative treatment.

The vertigo and DA control rate was evaluated by comparing the average number of vertigo events and DA events per month in the 6 months prior to ITG treatment with that of the average number in the 6 months after the treatment and before the first follow-up.

Statistical analysis

The statistical data were analyzed using SPSS 16.0 (SPSS, Inc., Chicago, IL). A Chi-square test, two independent samples *t* test, Mann–Whitney test, and paired *t* test were used to analyze the data and explore differences in the clinical features of MD patients with and without DAs. The level of significance was set at $p \leq 0.05$. Means are presented as mean ± standard deviation (SD).

Results

In the present study, 16 unilateral definite MD patients with DAs (9 males and 7 females; age, 38–71 years; age of onset, 33–68 years; duration of MD, 1–10 years, 11 left ears and 5 right ears) fulfilled the inclusion criteria. The clinical data of the DA group are presented in Table 2. In the control group, there were 161 unilateral definite MD patients without DAs (95 males and 66 females; age, 23–73 years; age of onset, 18–17 years; duration of MD, 0.1–20 years, 91 left ears and 70 right ears). There were no statistically significant differences in sex, age, affected side, and onset age between the DA group and control group (Table 3). However, the disease course in the DA group was significantly longer than that in the control group ($p = 0.007$, Table 3).

Hearing function

All the affected ears of MD patients in the two groups suffered from various degrees of sensorineural hearing loss. The mean threshold at 0.5, 1, 2, and 3 kHz was 68.25 ± 5.95 dB in the DA group (range from 55 to 78 dB, Table 3) and 58.48 ± 14.76 dB in the control group (range from 30 to 94 dB). The average hearing thresholds at low, middle, and high frequencies in the two groups are

Table 2 The clinical data of unilateral definite MD patients with DAs

Patient no.	Sex/age	Side	Course of MD (years)	No. of DA	PTA (dB)	MD stage	cVEMP	oVEMP	EH in vestibule	EH in cochlea			ITG
										CAT	CMT	CBT	
1	M/46	Left	3	2	65	3	85 dB	N	2 (63.98%)	2	2	2	–
2	F/65	Left	7	5	68	3	N	N	2 (68.44%)	2	2	2	–
3	M/45	Left	2	3	55	3	90 dB	N	2 (61.30%)	2	2	2	+
4	M/70	Left	2	5	76	4	N	N	1 (46.85%)	2	2	2	+
5	F/71	Left	3	13	67	3	–	–	2 (59.26%)	2	2	2	+
6	M/42	Left	4	8	67.5	3	90 dB	95 dB	2 (65.03%)	2	2	2	+
7	F/46	Left	6	6	67	3	85 dB	80 dB	2 (53.85%)	2	2	2	+
8	F/50	Left	10	7	60	3	N	N	2 (70.79%)	2	2	2	+
9	F/60	Left	8	2	65	3	85 dB	N	2 (53.63%)	2	2	2	+
10	M/58	Left	10	10	74	4	N	–	–	–	–	–	+
11	M/39	Left	1	1	55	3	85 dB	95 dB	2 (61.30%)	2	2	2	+
12	F/58	Right	2	2	68	3	90 dB	90 dB	2 (64.32%)	2	1	1	–
13	M/64	Right	2	8	78	4	N	N	2 (65.71%)	2	2	2	+
14	M/61	Right	5	3	65	3	N	N	2 (77.18%)	2	2	2	+
15	F/64	Right	10	3	69	3	80 dB	90 dB	2 (85.10%)	2	2	2	+
16	M/38	Right	5	3	72.5	4	90 dB	90 dB	2 (65.22%)	2	2	2	+

"–" means the patient did not receive the examination or treatment. In terms of EH in vestibule and cochlea, "1" means mild hydrops and "2" means significant hydrops, "+" means the patient received ITG

M male, *F* female, *MD* Meniere's disease, *DA* drop attack, *PTA* pure tone average (at 0.5, 1, 2, and 3 kHz), *cVEMP* the cervical vestibular-evoked myogenic potentials test, *oVEMP* the ocular vestibular-evoked myogenic potentials test, *N* no response, *EH* endolymphatic hydrops, *CA* cochlear apical turn, *CMT* cochlear middle turn, *CBT* cochlear basal turn, *ITG* intratympanic gentamicin.

presented in Table 3. MD patients with DAs showed significantly greater hearing loss than patients without DAs according to the two independent samples *t* test ($p = 0.000$, Fig. 1; Table 3). Significant differences at low frequencies and at middle frequencies are showed between DA group and control group in Fig. 1 ($p = 0.005$ and $p = 0.000$ respectively, Table 3). However, there was no statistically significant difference at high frequencies between the two groups (Fig. 1; Table 3).

Vestibular function

Nine patients in the control group and one patient in the DA group did not receive the cVEMP test, and 12 patients in the control group and 2 patients in the DA group did not undergo the oVEMP test. The outcomes of the cVEMP and oVEMP tests in both groups are shown in Table 3.

Patients in the DA group with a positive response in the affected ears showed no significant difference as compared with that in the control group, as shown by the Chi-square analysis of the cVEMP ($p = 0.542$) and oVEMP test ($p = 0.967$). The Mann–Whitney test revealed no significant difference in cVEMP threshold values ($p = 0.916$) and oVEMP threshold values ($p = 0.779$) between patients in DA group and patients in control group.

EH in the inner ear

Degrees of EH in cochlea and vestibule of inner ear were successfully evaluated in the affected ears of 15 MD patients in the DA group and 146 patients in the control group after bilateral intratympanic Gd injection. Fourteen patients in the control group and one patient in the DA group did not undergo MRI to evaluate EH, as this specific MRI test was not available for MD patients until 2014. In one case in the control group, the image obtained was poor and was excluded from the analysis.

In the DA group, except for one individual who presented with mild EH, all the other patients showed significant EH in vestibule (Table 2). The average area ratio of vestibular EH was 64.13%. All patients in the DA group had significant EH in cochlea (Table 2). In the control group, the quantity ratio of patients with none, mild and significant grade of EH was 5:42:99 in the vestibule, 4:40:102 in the cochlear apical turn, 4:43:99 in the cochlear middle turn, 8:57:81 in cochlear basal turn. The ratio of area of the endolymphatic space to vestibular space ranged from 21.12 to 80.12% (average 56.35%) in the control group. Figure 2 shows significant EH in the inner ear of case 13 in the DA group patient and mild EH in the inner ear of one patient in the control group. The area ratio of vestibular EH in the DA group was significantly higher than that in the control group ($F = 5.430$, $p = 0.008$).

Table 3 The variation in clinical features between the DA group and the control group

	DA group	Control group	*p* value
Gender			
Male	9 (56.25%)	95 (59.01%)	
Female	7 (43.75%)	66 (40.99%)	0.831
Age (years)	54.81 ± 11.02	52.05 ± 10.25	0.377
Side			
Left	11 (68.75%)	91 (56.52%)	
Right	5 (31.25%)	70 (43.48%)	0.345
Age of onset (years)	49.81 ± 11.04	48.63 ± 10.83	0.677
Duration of MD (years)	5.00 ± 3.16	3.42 ± 4.02	0.007
PTA (dB)	68.25 ± 5.95	58.48 ± 14.76	0.000
Low-tone hearing loss (dB)	66.72 ± 8.98	59.03 ± 15.76	0.005
Middle-tone hearing loss (dB)	68.44 ± 5.59	58.47 ± 14.89	0.000
High-tone hearing loss (dB)	72.50 ± 15.47	64.72 ± 18.94	0.114
cVEMP			
(+)	9 (60.00%)	103 (67.76%)	
(−)	6 (40.00%)	49 (32.24%)	0.542
Threshold of cVEMP (dB)	86.67 ± 3.54	86.51 ± 5.85	0.916
oVEMP			
(+)	6 (42.86%)	63 (42.28%)	
(−)	8 (57.14%)	86 (57.72%)	0.967
Threshold of oVEMP (dB)	90.00 ± 5.48	90.56 ± 5.40	0.779

The mean ± SD or number (%) of the relative data were showed

DA drop attack, *MD* Meniere's disease, *PTA* pure tone average (at 0.5, 1, 2, and 3 kHz), *cVEMP* the cervical vestibular-evoked myogenic potentials test, *oVEMP* the ocular vestibular-evoked myogenic potentials test, (+): have response, (−): absent

Statistically significant differences in the degree of EH in the apical turn ($p = 0.013$), middle turn ($p = 0.04$) and basal turn ($p = 0.005$) of the cochlea were respectively detected between DA group and control group, and EH in all turns of cochlea in the DA group were more severe as compared with that in the control group.

Outcomes of DA control following ITG treatment

The outcomes of DA control following ITG treatment are demonstrated in Table 4. The follow-up period of 13 unilateral definite MD patients in the DA group ranged from 6 to 54 months (mean 21.08 months). Eleven patients (84.62%) achieved complete control of vertigo (Class A). One patient (7.69%) achieved good vertigo control (Class B), and one patient (7.69%) obtained limited control of vertigo (Class C). No patient had control of vertigo in Class D or F. DA recurrence was closely correlated with vertigo control after ITG treatment. Symptoms of DAs disappeared in all Class A patients. The Class B patient complained of controllable falls after ITG treatment. This patient was able to forecast these falls and leant against the wall or something close by to prevent himself from the sudden injury. The DA episodes without warning did not reduce satisfaction of the Class C patient. No patients complained of significant hearing loss following ITG treatment.

Discussion

In the present study, the clinical features of unilateral definite MD patients were retrospectively analyzed to identify variations in MD patients with and without DAs. The incidence of DA events originating from MD in the 177 unilateral definite MD patients was 9.04% in our study. Sudden falls without warning can provoke serious injuries or fractures in MD patients with DAs, especially among the elderly [22]. Elders with MD are thought to be predisposed to DAs [23]. However, in terms of the age or onset age in MD patients, we found no difference between MD patients with and without DAs. Only three (18.75%) of 16 MD patients in the DA group were older than 65 years. The youngest MD patient with DAs was only 38 years old. DAs also expose young and

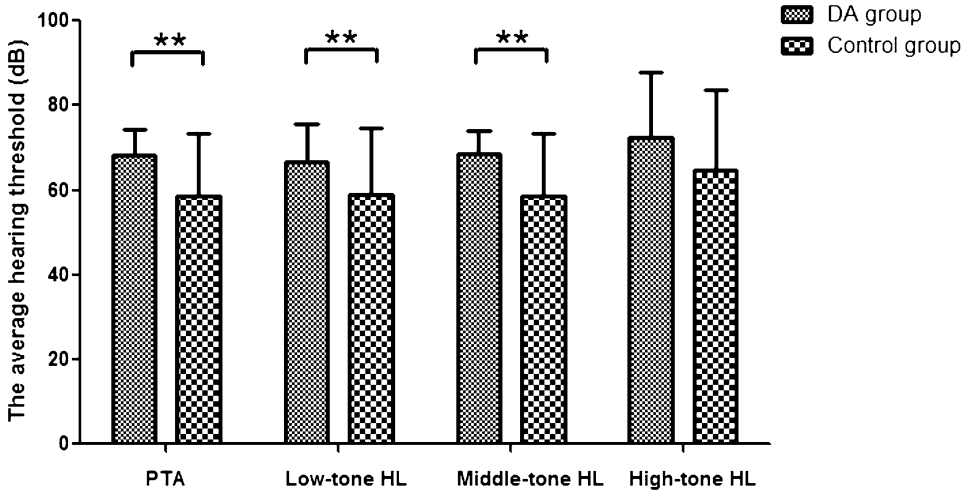

Fig. 1 The statistical analysis of hearing function in the drop attack (DA) and the control group. Significant differences of pure tone average threshold (PTA), low-tone hearing loss (HL) and high-tone HL was demonstrated between the DA group and the control group ($p < 0.01$). There was no statistical difference at high frequencies between the two groups ($p > 0.05$) (**$p < 0.01$)

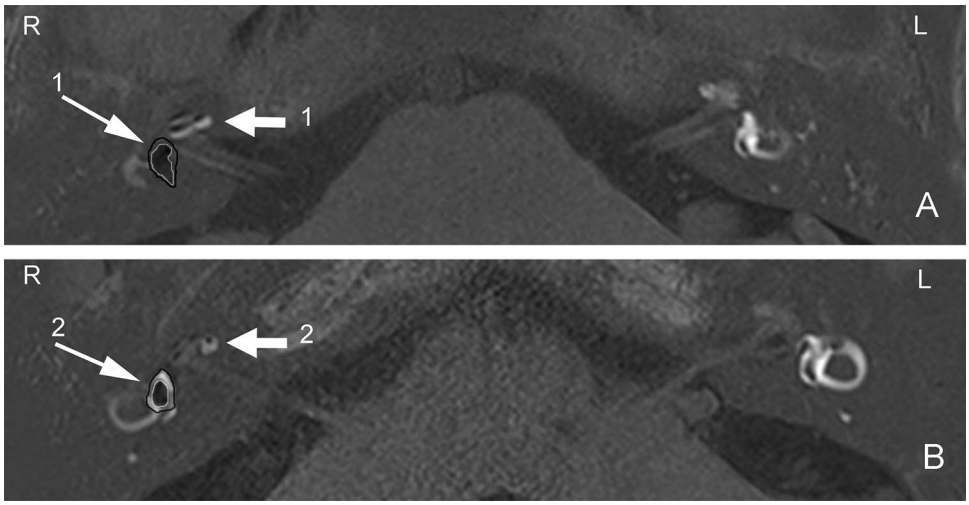

Fig. 2 Three-dimensional real inversion recovery magnetic resonance imaging (3D-real IR MRI) images of two patients with right Meniere's disease (MD) in the drop attack (DA) group and the control group. **a** Case13 MD patient in the DA group. Relative high signal in both inner ears reveals that gadolinium (Gd) successfully diffused in perilymph. The large negative signal space diluting to perilymphatic space in right inner ear indicates significant endolymphatic hydrops (EH). The area ratio of the endolymphatic space (white line area) in vestibule (thin arrow) to the vestibular space (black line area) is 65.71%. The thick arrow shows significant EH in all turns of cochlea in right inner. The left inner ear was displayed a normal endolymphatic space. **b** A MD patient in the control group. Relative high signal in both inner ears reveals that successfully diffused in perilymph. Thin arrow indicates mild EH in vestibule of right inner ear and the area ratio the endolymphatic space (white line area) to the vestibular space (black line area) is 43.31%. Mild EH were also observed in all turns of cochlea in right inner ear (thick arrow). The left inner ear was presented without enlargement of endolymphatic space

Table 4 Efficacy of ITG on 13 unilateral MD patients with DAs

Patient no.	The follow-up period (months)	Class of vertigo control	The number of DA		PTA of affected ear (dB)	
			Before ITG	After ITG	Before ITG	Three weeks after ITG
3	26	A	3	0	55	47.5
4	17	A	10	0	76	72.5
5	7	A	13	0	67	–
6	14	A	8	0	67.5	44.4
7	22	A	6	0	67	63.1
8	6	C	7	6	60	–
9	25	A	2	0	65	55.3
10	54	A	16	0	74	66.9
11	16	A	1	0	75	62.5
13	17	B	8	5[a]	78	72.5
14	37	A	3	0	65	58.8
15	12	A	3	0	69	–
16	20	A	3	0	72.5	–

"–" Means the patient did not receive the audiometric assessment

ITG intratympanic gentamicin, *MD* Meniere's disease, *DA* drop attack, *PTA* pure tone average (at 0.5, 1, 2, and 3 kHz)

[a]A controllable fall

middle-aged patients to a multitude of dangers. Therefore, clinicians should never ignore the seriousness of DAs among MD patients in any age group.

Controversial surrounds the timing of the first DA episode (i.e., whether it occurs early, late, or at any time in the course of MD). Most reports support the idea that DAs are

of late onset in the course of MD [1, 2, 23]. Janzen et al. [4] reported that the timing between the onset of MD and first appearance of a DA varied from 3 to 20 years in MD patients with DAs, and Baloh et al. [3] concluded that the timing was less than 1–29 years. In our previous study [20], we demonstrated that MD patients suffered from gradual deterioration of EH with disease progression and that the vast majority of MD patients suffered severe vestibular EH after their second year of the disease. Meanwhile, the duration of the disease in MD patients with DAs was significantly longer than that in patients without DAs. Except for one patient, all the MD patients with DAs experienced symptoms of DAs at least 2 years after the onset of vertigo. In addition, MRI revealed significantly greater degrees of EH in the vestibule and all turns of the cochlea in the DA group than in the control group. Therefore, we speculated that DAs tended to occur in the stage when the severity of EH in the inner ear worsened.

In terms of hearing function, MD patients with DAs showed a significantly worse PTA threshold than patients without DAs in our study. Hearing loss was also associated with the extent of displacement of Reissner's membrane in all turns of the cochlea [20]. This may be attributed to the longer disease course and the significant degree of cochlear EH in the DA group as compared with that in the control group. However, this result was inconsistent with that of another study [8], which indicated that there was no statistically significant difference in the hearing levels of affected ears in MD patients with and without DAs. This discrepancy of hearing function in affected ears may stem from the specific criterion used by the study, which excluded MD patients with advanced stage MD. Their finding of worse hearing levels in the asymptomatic ear highlights the possibility that patients in the DA group may have a high risk of progressing to bilateral MD. High-tone hearing loss has no statistic significant difference between the DA group and control group. The finding may be associated with age-related high-tone hearing loss.

The mechanism of DAs secondary to MD was thought to be an abrupt mechanical deformation of the otolithic membrane due to high endolymphatic pressure and stimulation by saccular and/or utricular signal activating vestibule-spinal reflex pathways [3]. This resulted in loss of postural tone and balance. The function of otolithic organs is thought to play a key role in the whole process of DA episodes. The cVEMP is widely considered an efficient way to determine saccular function and the vestibulo-collic pathway [24]. Whereas the oVEMP reflects utricular function and the otolith-collic reflex pathway [25]. In our study, all the patients in the DA group showed abnormal VEMPs. However, there was no significant difference in either saccular function or utricular function between MD patients with DAs and without DAs, despite the significantly greater degrees of vestibular EH in the DA group. The findings on cVEMP (saccular function) is in agreement with those of a previous study by Huang et al. [26] who compare cVEMP results of MD patients with and without DAs. However, they come to the opposite conclusion as regards oVEMP (utricular function) results. The discord may be explained by the small sample size. Their study consisted of 10 age- and sex-matched definite MD patients as control group from 180 MD patients. In the present study, there were no differences between the DA group and control group in sex, age, and affected side of the patients. Timmer et al. [27] reported that the threshold of cVEMP was more likely to be absent in the affected ear of MD patients with DAs. However, they did not eliminate factors, such as patients' ages and MD stage that could have various effect on the assessment of vestibular function. In accordance with our findings on vestibular function and EH degrees, we speculate that the function of the otolithic organ in MD patients with DAs may not be completely abolished and that it is sensitive to some unexpected stimulating signals, such as a sudden change of endolymphatic pressure.

DA presenting as a sudden fall without any warning is too dangerous to ignore and requires an effective treatment. In the present study, 92.31% of 13 refractory definite MD patients with DAs (Class A and Class B patients) achieved satisfactory vertigo and DA control. Furthermore, the control of DAs after ITG treatment was in parallel with vertigo control. The effects of gentamicin on the control of DAs may be associated with its vestibulotoxicity, which shows a similar mechanism of vertigo control. This finding indicates that gentamicin can play a role in controlling DAs. A previous study showed a completed control rate of DAs in 83.3% after the first injection of gentamicin [10] which is close to our Class A control data (84.62%). Nowadays, the other destructive treatments, such as labyrinthectomy and vestibular neurectomy, were barely applied to MD patients, because of their serious side effects. Liu et al. [9] supported that intratympanic dexamethasone injection (ITD) should be the primary treatment for MD patients with DAs, and DAs in 71.4% cases disappeared after initial ITD treatment. However, according to the clinic feature of DA patients in our study, DA group patients tend to suffer from a long course of vertigo, severe hearing loss, a significant degree of EH, but uncompleted abolished vestibular function. To these refractory and life-threatened DA patients, the relative safe and aggressive treatment (ITG), which decreases vestibular function, is much more appropriate. Hearing loss following single-shot intratympanic low-dose gentamicin may not be a major issue for intractable MD patients. First, nearly all MD patients with DAs suffer from severe hearing loss with significant cochlear EH. Anatomically, the cochlear aqueduct is located close to the round window. As gentamicin enters the perilymph through the round window and oval window, it can be eliminated through the cochlear aqueduct before spreading along the scala tympani. Its level is then diluted

by CSF [28]. In our study, none of the patients suffered from aggravated hearing loss after ITG treatment. However, long-term hearing assessment after ITG treatment remains to be analyzed.

Conclusion

DAs tend to occur in MD patients with a long course of vertigo, severe hearing loss and a significant degree of EH in the inner ear. The present study indicates that the function of the otolithic organ may not be completely abolished and that it is sensitive to stimulating signals, despite of the severe vestibular EH in MD patients with DAs. In this study, 92.31% refractory definite MD patients with DAs achieved satisfactory vertigo and DA control after a single injection of low-dose gentamicin. ITG, which results in decreased vestibular sensitivity, was an effective treatment for MD patients with DAs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the present study involving human participants were approved by the medical ethics committee of the Eye, Ear, Nose & Throat Hospital and in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All patients included in the study signed the informed consent. For this type of study formal consent is not required.

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